REMARKS

Claims 1, 2 and 8-16 are pending in the present application. Claims 1, 2, 11 and 16 have been rejected. Claim 1 has been amended to more clearly articulate the claims of the present invention. Support for said amendment is found in Applicants' specification page 7, lines 11-13 and line 35 and page 10, line 1. Accordingly, claims 2, 11 and 13-15 have been canceled. Claims 8-10, 14 and 15 have been withdrawn from consideration. No new matter has been added.

ART REJECTIONS

REJECTIONS UNDER 35 USC §102

Claims 1 and 11 have been rejected under 35 USC §102(b) as being anticipated by Juhasz et al. (Proc. Nad. Acad. Sci. USA, Vol. 91, pp.4333-4337) (hereinafter "Juhasz"). As set forth in the record, the Office states that Juhasz teaches a method for determining the molecular weights of highly acidic compounds complexed with basic polypeptides and is equal to the steps and elements of claims 1 and 11. Applicants respectfully traverse this rejection.

In light of the amendments, Applicants believe the rejection is now moot. Applicants submit that Juhasz describes a way of using *non-covalent* interactions to improve ionization and detection of the molecular weights of strongly acidic components. Juhasz fails to teach covalently modifying peptides or proteins and additionally fails to describe the generation of fragmentation patterns that facilitate sequencing of the peptide or protein. Without the covalent linkage of the negatively charged group to the peptide/protein ion, the complex dissociates on ionization and no sequencing benefit is observed. *See*, Juhasz, p. 4336, Col. 1, ¶ 3 (following "Structure I"). Applicants respectfully submit that anticipation can only be established when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention. *RCA Corp. v. Applied Digital Data Sys., Inc.* 221 USPQ 385, 388 (Fed. Cir. 1984). Thus, there must be no difference between the claimed invention and the disclosure relied upon as anticipatory, as viewed by a person of ordinary skill in the filed of the invention. *Scripps Clinic & Res. Found. v. Genentech Inc.*, 927 F2d 565, 18

USPQ2d 1001 (CAFC 1991). Simply because the references relate to the same area of technology is insufficient.

Because Juhasz fails to teach each and every element of Applicants' presently claimed invention, specifically the covalent modification of the proteins or peptides, the rejection under 35USC §102(b) is improper. Applicants are claiming a method for enhanced *sequencing* not "remarkable sensitivity" for detection of a parent ion as described in Juhasz.

In light of the foregoing, including the amendment herein, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §102(b).

REJECTIONS UNDER 35 USC §103

Claims 1, 2, 11 and 16 have been rejected under 35 USC §103(a) as being made obvious by Spengler et al. (International Journal of Mass Spectrometry and Ion Process, 1997, Vol. 169/170, p.127-140) (hereinafter "Spengler") in view of Itoh et al. USP 4,835,312 (hereinafter "Itoh") and further supported by Ness et al. USP 6,027,890 (hereinafter "Ness"). As set forth in the record, the Office believes it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice the invention of Spengler using sulfonic acid taught by Itoh where the motivation would have been to use derivatizing reagents that minimize side-chain reactions as taught by Itoh thereby increasing spectral resolution. Additionally, the Office believes that motivation for the use of sulfonic acid to improve mass spectral analysis is provided by Ness who teaches the use of sulfonic acid to increase the relative sensitivity of an analyte being detected by mass spectrometry. Thus, the Office has concluded that one of ordinary skill in the art would have had a reasonable expectation of successfully combining the method of Spengler using sulfonic acid derivatives taught by Itoh in view of Ness. Applicants respectfully traverse this rejection.

In light of the amendments, Applicants believe the rejection is now moot. Applicants submit that Spengler discloses cationic derivatives as means for improving peptide sequencing. Cationic derivatives, however, require higher energy for the fragmentation that is needed to generate ions for sequencing and leads to very complex

fragmentation patterns, including a-, b- and often y-ions that are difficult to interpret. While cationic derivatives may improve peptide detection *sensitivity*, their use tends to reduce fragmentation. The present invention utilizes anionic derivatives requiring lower energy for fragmentation and results in more efficient fragmentation and easily interpreted fragmentation patterns. The resulting pattern is further simplified by the negative charge on the N-terminal fragments suppressing the detection of the fragment ions containing the N-terminus and primarily a single set of C-terminal y-ions. (*See also*, Applicants specification, page 16, lines 8-19, discussing the method of the present invention producing spectra that are substantially free of a-ions and b-ions).

Itoh fails to rectify the shortcomings of Spengler. While it is a goal of Itoh to provide a production process, which is substantially free of side reactions to produce an intended N-substituted amide compound with good selectivity, the conditions of the synthesis disclosed fail to provide for the utilization of biological peptides and protein samples as presently claimed by Applicants. Thus, there is no motivation to use the cationic derivatives described in Spengler with the production process disclosed in Itoh to arrive at the presently claimed invention.

Furthermore, Ness also fails to remedy the shortcomings of the cited references. Ness describes methods for detecting the binding of a first member to a second member of a ligand pair. Anionic derivatives are merely used to incorporate a charge into the tag in order to increase the *sensitivity* of its detection by the mass spectrometer since it is widely known that the mass spectrometer only detects ions with a net charge. Ness, however, fails to teach or suggest the use of anionic derivatives to improve fragmentation of a peptide or protein to aid in its identification.

In view of the foregoing it is clear that the cited references alone or in combination fail to meet teach or suggest the elements of the presently claimed invention. In determining obviousness, the entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered. *See, In re Wright*, 848 F.2d 1216, 6 USPQ2d 1959, 1961, 1962 (Fed. Cir. 1988). The fact that the references relate to the same area of technology is insufficient. *In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

Applicants submit that all of the references combined, still fail to remedy the sequencing of polypeptides for improved fragmentation and mass spectra that can be easily interpreted. When prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved does not satisfy the criteria of 35 USC §103 for precluding patentability. *Lindeman Maschinenfabrick GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103(a).

CONCLUSION

In view of the above, Applicants respectfully submit that each of the issues raised by the Office Action has been addressed. Reconsideration and allowance of each of the pending claims is respectfully requested.

Respectfully Submitted,
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